Asymptomatic malaria in the etiology of iron deficiency anemia: a nutritionist’s viewpoint

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An acute episode of malaria usually precipitates anemia of a varying severity which, in extreme cases, can be fatal. This post-malarial anemia has the characteristics of iron deficiency anemia (IDA). It results largely from a redistribution of iron because there is minimal iron excretion after the lysis of infected (and uninfected) red cells caused by malaria. Instead, the potentially toxic hemoglobin released when the erythrocyte ruptures is complexed to haptoglobin and hemopexin. The haptoglobin-hemoglobin complex is recognized by specific receptors on circulating macrophages (CD163) and internalized. The iron-loaded macrophages migrate to the reticuloendothelial system where they can lodge for long periods of time. The hemopexin-heme complex undergoes receptor-mediated uptake by liver cells where again the iron can persist for a long time.

These processes also play a major role in the anemia of chronic disease and are part of an integrated acute-phase response that has evolved—it is assumed—to maintain body iron and yet prevent iron-catalyzed free-radical damage and to sequester it safely beyond the reach of (most) potentially pathogenic bacteria. Bacteremic septicemias are commonly precipitated by malaria (eg, reference 1) and may be a major cause of mortality. Of all the essential micronutrients, iron appears to be by far the most critical mediator of this battle between the human host and its pathogens and hence must be very carefully chaperoned and stored (2).

Malaria is a strongly inflammatory disease, and while the inflammation persists the recycling of sequestered iron from the liver and macrophages remains blocked (3). In the immediate aftermath of acute malaria it is this redistribution of body iron that is central to the iron-limited suppression of erythropoiesis because, under normal circumstances, ~95% of the iron supply to the erythron comes from recycled iron and only 5% from recent absorption from the diet (4). In malaria, and during early convalescence, the erythropoietic drive usually remains high (signaled by raised erythropoietin), but erythropoiesis is often, although not always, impaired [signaled by low soluble transferrin receptor (sTFR) and reticulocyte levels]. In the absence of a sufficient iron supply, there is microcytosis and an increase in the proportion of porphyrin moieties in which zinc is substituted for iron, thus creating elevated concentrations of zinc protoporphyrin (ZnPP). Raised ZnPP is normally interpreted as indicating iron deficiency; it is considered to be independent of confounding affects of inflammation, but in actuality reflects functional iron supply to the erythron, a subtle but important difference. Intriguingly, ZnPP may have additional antimarial effects (5).

A further mechanism to deplete the systemic circulation of iron is by blocking intestinal absorption. This contributes to the longer-term anemia common in malaria-endemic areas, especially because diets in these regions tend to contain low amounts of iron, very low amounts of heme-iron, and high amounts of phytates and polyphenols.

Tracer studies using Fe⁵⁷ and Fe⁵⁸ in Gambian children showed that iron absorption was suppressed by 67% immediately after treatment of acute malaria and by 35% a fortnight later, compared with matched IDA cases without malaria (6). In this issue of the Journal, Cercamondi et al (7) report a very similar suppression of iron absorption in young Beninese women with asymptomatic malaria parasitemia.

The Cercamondi study used a combination of oral Fe⁵⁷ mixed with a sorghum-based meal followed by an intravenous infusion of Fe⁵⁸—a powerful approach that estimates both intestinal iron absorption and the systemic utilization rate of iron. Twenty-three nonpregnant women with asymptomatic malaria (defined as an asexual Plasmodium falciparum parasitemia of >500/μL blood) were studied over 14 d, then treated and restudied 14 d later. Surprisingly, the women had very high concentrations of hemoglobin for a malaria-endemic area (134 g/L), and only 2 (9%) met the criteria for IDA. There was no separate control group. Intestinal iron absorption averaged 10.2% while infected and 17.6% after treatment. Systemic iron utilization (83–85%) was not altered. The Gambian trial assessed red cell incorporation (a composite measure of absorption and utilization) and found values of 8.7% immediately after acute malaria (compared with 26.6% in matched anemic controls without malaria) and 15.5% a fortnight later (6). These values are astonishingly close to the Benin data once the absorption and utilization figures are compared.
bined. The Gambian children (mean hemoglobin: 83 g/L; 100% IDA) were much more anemic than were the Benin women, so a greater incorporation rate would have been expected after recovery (note the value of 26.6% in the nonmalarial controls), which indicates either a greater residual effect of a clinical episode of malaria or a less robust recovery in young children.

Cercamondi et al (7) analyzed a range of inflammatory markers (C-reactive protein and inflammatory cytokines) as well as markers of iron status (ferritin, iron-binding capacity, serum iron) and erythropoietic drive and activity (erythropoietin, growth differentiating factor-15, and sTfR). They also assessed hepcidin. Hepcidin is a heptatic-derived peptide hormone that appears to be the “master” regulator of iron homeostasis acting through the suppression of iron egress from enterocytes and macrophages by blocking ferroportin (8). Previous studies have shown it to be raised in malaria (eg, reference 9).

These markers showed that the improved iron absorption coincided with a reduction in inflammation after clearance of the parasitemia and with a 50% reduction in hepcidin (7). However, cross-sectional associations between hepcidin and iron absorption were only apparent in the noninfected state, showing that there is still much to learn about the role of hepcidin in modulating iron absorption in different diseases. In the meantime it is worth noting that such a life-critical process as regulation of duodenal iron absorption is likely to have a series of back-up mechanisms, and it is known that tumor necrosis factor-α can block iron absorption through a hepcidin-independent mechanism (10) and that this is also a contributor to malaria-associated iron deficiency anemia (11).

A detailed examination of Cercamondi et al’s (7) study reveals a few intriguing questions that point to the complexities of iron-malaria interactions and the need for further research. First, how did the subjects manage to maintain such high hemoglobin concentrations despite active parasitemia, and why did hemoglobin fall slightly after treatment? Second, why were there inconsistent correlations of iron absorption with iron and inflammatory markers in the infected and treated states, and why did hepcidin not correlate with absorption during infection?

There are many parallels between the Benin and Gambian studies, both of which confirm the inflammatory response as mediator of the suppressed incorporation of iron, and they help clarify mechanisms by which malaria worsens the burden of anemia. Together, they pose significant challenges to the development of programs for iron administration in malaria-endemic areas—a topic that is already high on the global nutrition agenda after the adverse effects of iron supplementation noted in the now-infamous Pemba trial (12). The Gambian study challenges the wisdom of coprescribing iron when treating malaria, and the authors of the Benin study claim that their observations may help explain why food fortification with iron has so far yielded disappointing results in Africa (7). However, the accompanying editorial in this issue of the Journal (13) from a malariologist’s viewpoint questions the extrapolation of the Benin study, based as it was on a very small subset of women with the highest parasite counts and most of whom were not anemic.

A unifying solution, which might be a necessary antecedent of successful iron interventions in many of the world’s poorest nations, would be the elimination of malaria. Progress toward this goal is patchy but shows some evidence of remarkable success.

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REFERENCES